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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
Center for Biologics Evaluation and Resea
1401 Rockville Pike
Rockville MD 20852-1448

November 17, 1997

WARNING LETTER

CBER-98-004

CERTIFIED MAIL - RETURN RECEIPT REQUESTED

Elsebeth Budolfsen
President
Allergologisk Laboratorium, A/S
Bøge Allé 10-12
DK-2970 Horsholm, Denmark

Dear Ms. Budolfsen:

The Food and Drug Administration (hereafter "FDA" or "the agency") conducted an inspection of your facility located at Bøge Allé, DK-2970 Horsholm, Denmark, between September 8 and 12, 1997. During the inspection, FDA investigators documented the following violations of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (FD&C Act), and Title 21 Code of Federal Regulations (21 CFR), Parts 600 and 211:

1. Failure to assure that each lot of dried product is tested for residual moisture and meets the established limits as specified in standard operating procedures [21 CFR 610.13(a)(1)] in that, between July 1994 and March 1997, at least nine lots of venom extract failed the initial test for residual moisture (Karl Fischer Test) due to low recovery volume; however, the results were accepted and the products were released.

2. Failure to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)], in that, the calculation factor that was instituted in order to adjust for the insufficient supernatant recovery in the initial test for residual moisture of lyophilized allergenic extracts was not validated, nor was the retest modification included in the standard operating procedure.

3. Failure to routinely calibrate, inspect, and check automatic, mechanical, or electronic equipment used in the manufacture, processing, packing, and holding of a drug product

according to a written program designed to assure proper performance [21 CFR 211.68(a)] in that:

a. there are no defined specifications for chamber temperature, condenser temperature, or product temperature of the lyophilizers;

b. a temperature distribution study to assure that all shelves of the lyophilizers reach and maintain a uniform temperature during freeze drying operations has not been performed ;

c. there are no established load patterns for the two autoclaves used for sterilization of closures, media, and equipment used in the production of allergenic extracts;

4. Failure to investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed [21 CFR 211.192] in that, between July 1995, and August 1997, the final containers from seven of [redacted]oads lyophilized using program 81 failed the initial residual moisture testing; however, no investigation of the lyophilization process was initiated.

5. Failure to establish and follow written procedures, standards or specifications, methods of testing, methods of cleaning, sterilizing, and processing to remove pyrogenic properties from drug product containers and closures [21 CFR 211.94(d)] in that, there are no procedures in place to reduce or eliminate pyrogens from closures used for allergenic extracts.

6. Failure of the quality control unit to approve or reject all procedures or specifications impacting on the identity, strength, quality, and purity of drug products [21 CFR 211.22(c)] in that, the lyophilization load of Honey Bee Venom, batch 6657/621354, exceeded the shelf temperature specification but was accepted and released.

7. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile and to assure that such procedures include validation of any sterilization processes [21 CFR 211.113(b)] in that:

a. monitoring of the Water For Injection (WFI) system between June 1996, and August 1997, revealed at least 25 instances where microbial action limits were exceeded; however, corrective action such as sanitization was not taken;

b. established procedures for the WFI system require sanitization only after microbial action limits are exceeded on five consecutive occasions following the initial actionable sample result;

c. WFI piped directly into the vial washer used for cleaning final product containers in room [redacted] is not sampled for microbial contamination;

d. personnel were observed sampling the WFI system at the drop point identified as "Hane F", by taking off the metal lid of the reservoir storage tank, and removing a scoop of water using a metal ladle. Water from this storage tank is used to supply a boiler, which in turn is used to sterilized the autoclave and the lyophilizers.

8. Failure to establish separate or defined areas or other control systems for manufacturing and processing operations to prevent contamination or mixups [21 CFR 211.42(c)] in that:

a. monitoring of positive pressure for the aseptic core areas relies on an alarm system which is activated when pressures in adjacent rooms are of equal or lower values. In 1997, there were 53 instances of alarm activations; 35 of which were for "both doors open" in room [redacted]

b. environmental monitoring of personnel is not performed before and after every filling operation; rather, filling operators are monitored every 14 days;

c. quantitative microbial monitoring (slit sampling) was observed as having been performed at an inappropriate distance from the filling operation;

d. qualification of HEPA filters and laminar flow hoods used in the aseptic core has not been performed since April 1996.

9. Failure to maintain or follow written procedures for cleaning and maintenance of equipment including utensils, used in the manufacture, processing, packing, or holding of a drug product [21 CFR 211.67(b)] in that:

a. there are no standard operating procedures (SOPs) for maintenance and revalidation of the autoclave;

b. SOP [redacted] a does not define "extra cleaning", which is done under certain circumstances when environmental monitoring action limits were exceeded. In addition, the "extra cleaning", when performed, is not documented in the cleaning log.

10. Failure to maintain buildings used in the manufacture, processing, packing, or holding of a drug product in a good state of repair [21 CFR 211.58] in that, leaking was observed from three of [redacted] stills of the Hafer WFI unit.

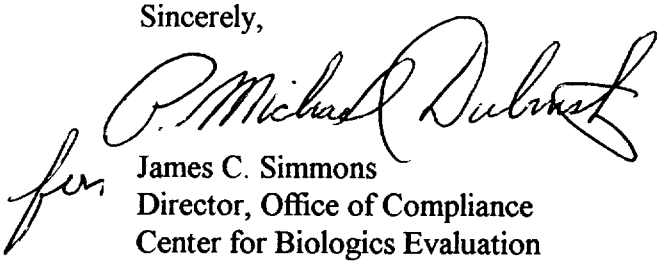
11. Failure to establish and implement a written testing program designed to assess the stability characteristics of drug products [21 CFR 211.166] in that, there is no stability program for standardized allergenic extracts.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deficiencies at your establishment. It is your responsibility as management to assure that your facilities are in compliance with all of the provisions of the Federal Food, Drug and Cosmetic Act and all applicable regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

We acknowledge receipt of your response dated October 3, 1997, to the Form FDA 483 issued at the close of the inspection. The promised corrective actions appear to adequately address the deviations observed and may be referenced in your response to this letter. Please submit in writing, within 15 working days of receipt of this letter, your responses to the violations identified in this letter and a detailed report describing the status of all corrective actions outlined in your October 3, 1997 letter. Failure to promptly correct the deviations noted may result in regulatory action, such as license suspension and/or revocation, without further notice.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, please contact Anita Richardson at (301) 827-6201.

Sincerely,



for James C. Simmons
Director, Office of Compliance
Center for Biologics Evaluation
and Research